Glycogen Metabolism

Introduction

To this point, we've considered the liver in two states—insulin-dominant and glucagon-dominant—and separated those two states into either insulin-glycolysis or glucagon-gluconeogenesis. It would make sense, however, if there were some stored form of rapidly accessible glucose which could be used during times of hypoglycemia. The long-term stored form is adipose, which gets burned as fatty acids to acetyl-CoA and NOT glucose. But because eating patterns vary, and both glycolysis and gluconeogenesis require induction of genes, the body has created a temporizing storage form within cells that can be accessed quickly. That's **glycogen**. Glycogen is a series of **glucose molecules** stuck one to the other, packaged in extremely dense packets of **branching chains**. Don't confuse the branched chains of glycogen (glucose) with branched-chain amino acids. They're totally different things.

Glycogen is stored in the liver in **large granules** (i.e., there's a lot of it) to be rapidly consumed and distributed to all other tissues. The liver is still doing its job—supplying glucose to every cell. Only in addition to building new glucose (gluconeogenesis), it can also rapidly release already-made glucose stored as glycogen. That's the cool thing about glycogen. It's literally just a **string of glucose molecules attached to each other**. Break just one bond and bam, a glucose (with a phosphate) is ready to go.

Other cells can store glycogen, too. **Muscle cells** store a good amount. Muscle cells don't ONLY take up and burn glucose. They take up, burn, and sometimes store glucose for later. The muscle cells can't release the glucose into circulation. They can only use the glycogen they have in them for themselves. This makes especially good sense for muscle that may not be contracting all the time—no extra energy is needed at rest. And having a rest period, they have an opportunity to store some energy. Later, when the muscle contracts, it'll have a local supply (within itself) of glucose that's independent of hormones or other organs. In times of immediate need—running away from a predator—there wouldn't be time for the liver to realize that the muscles needed the extra boost. And since the liver is responsible for global homeostasis, if only the calf muscles needed more glucose the liver wouldn't know until the T. rex ate you. (If you stay absolutely still a T. rex can't see you; running was your first mistake.)

Cells that are **always working**, the ones that are **metabolically active** like the **heart**, **brain**, and **kidneys**, the ones most vulnerable to poor perfusion, essentially have no "downtime" during which they could store glycogen. Learn them as "no glycogen."

Most glycogen is stored in the liver, because that stored glycogen is for the entire body during global hypoglycemia, a holdover while gluconeogenesis revs up. Muscles have some glycogen, because they need it when they need it, but aren't maximally active all the time. Brain and heart are always active, so have no time to store glycogen. While adipose does have glycogen, learn adipose as "stores triglyceride" rather than "could have glycogen or triglyceride."

Glycogen Structure

Glycogen is built on a **core protein**. Then long chains of glucose attach end to end, the **1 position** of the newest glucose in the chain attaching to the **4 position** of the previous. This is called an **α-1, 4-glycosidic bond**. If there were only single chains of glucose that stuck straight out, having grown out from the core, the density of the glucose would be greatest at the center. The farther out from the center of the circle, the more space there would be between the straight chains. Take two pens. Hold them in the shape of a V with your index finger and thumb. The pens are close together at the point of the V, in a smaller volume, so have a higher density there. Moving toward the periphery, they increasingly diverge from each other. Wouldn't it be smart to fill that space?

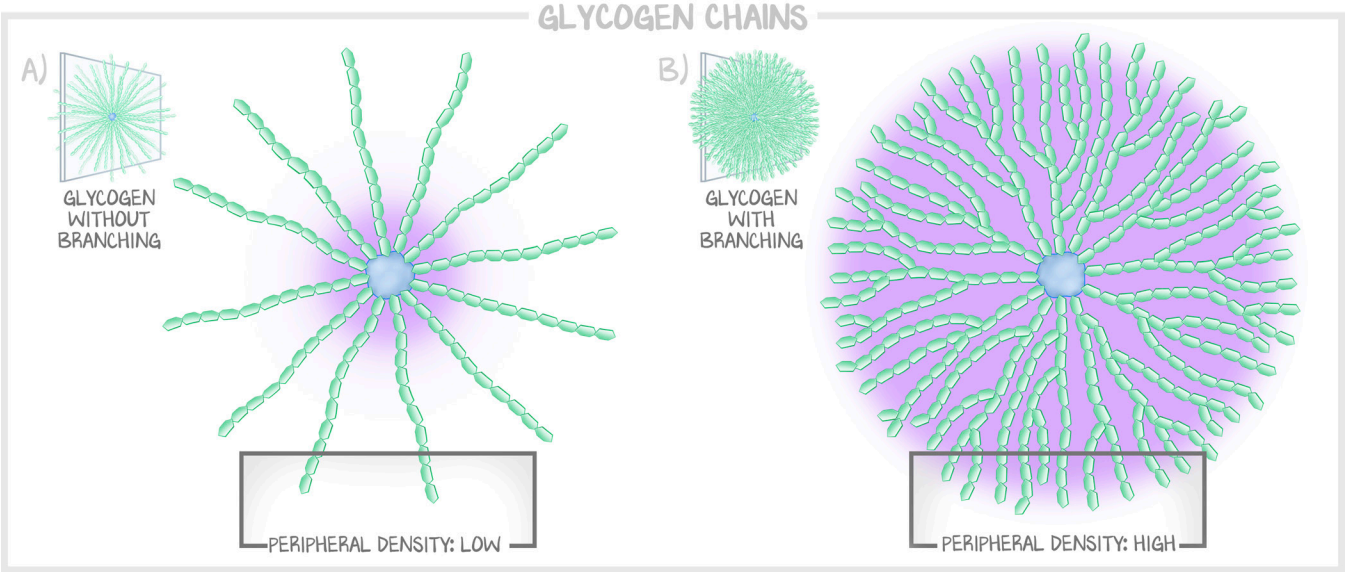

Figure 11.1: Glycogen Chains
(a) Without branched chains, the density of glucose away at the periphery is low, whereas with branching enzymes (b), the density of glucose is quite high on the periphery.

In addition to straight chains of glucose, glycogen also has branches. These branches occur between the **1 position** of the incoming glucose and the **6 position** of the glucose already on the chain. This is called an **α-1,6-glycosidic bond**.

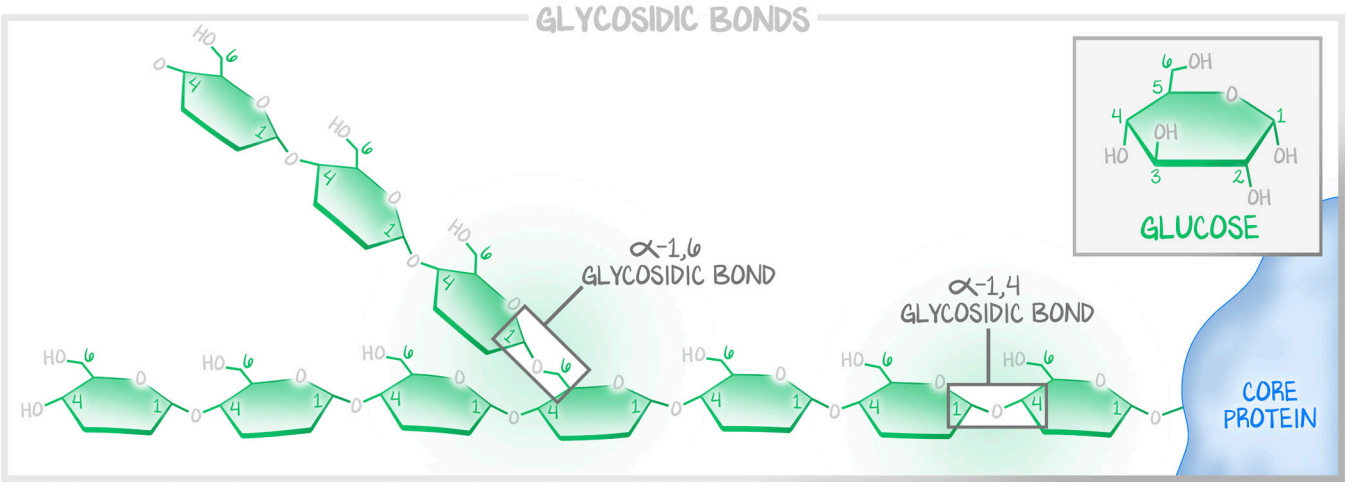

Figure 11.2: Glycosidic Bonds
1,4 = straight chain; 1,6 = branch.

When a chain branches, the original straight chain and the 1,6 branch can both continue to elongate through 1,4 bonds. Then both can branch again. When this branching occurs, what happens is that all of the space "between the pens" is filled with straight chains. The farther from the center of the circle (your index and thumb) the more space between the original chains (the pens). And if glycogen is working right, all of that space will be used. Which means, while with **only straight chains the density was greatest at the center**, with real glycogen, **with straight and branching chains the density of glucose is greatest at the periphery**. If the point is rapid mobilization of glucose, having the most available at the periphery, with the fastest access, makes the most sense. More can be mobilized, faster.

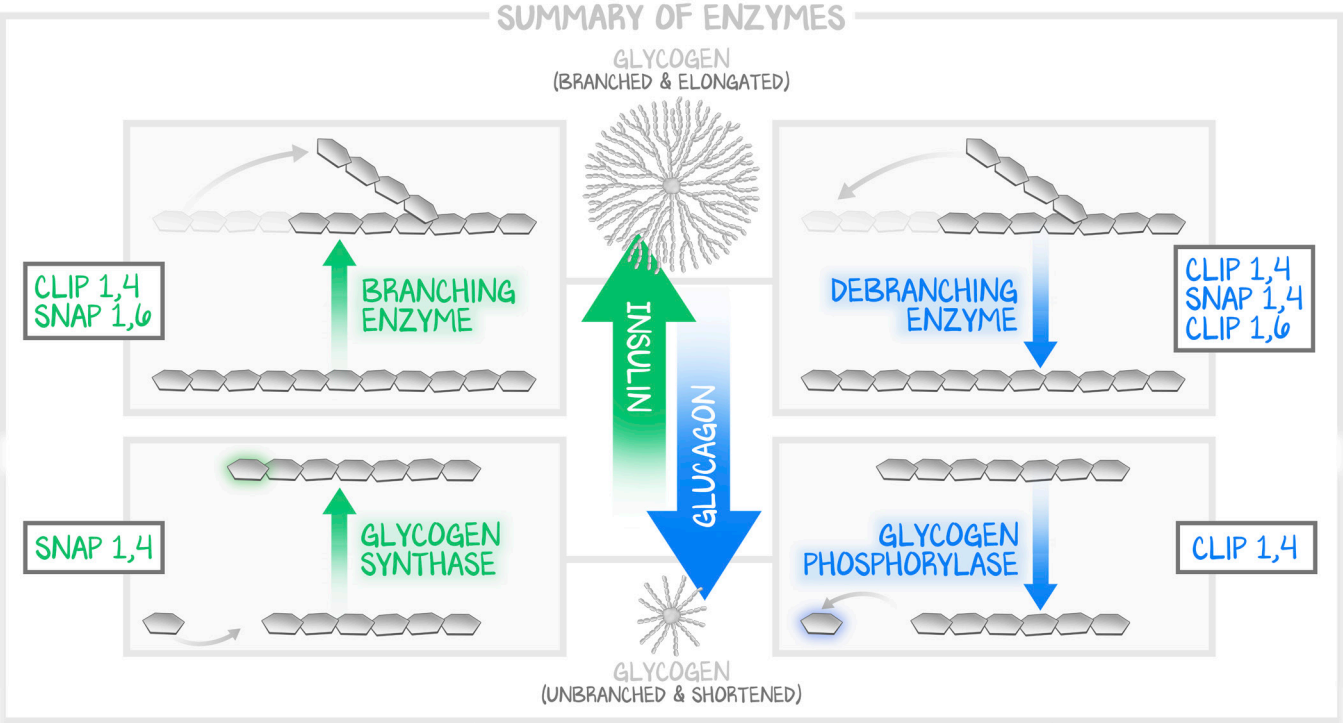

Figure 11.3: Summary of Enzymes

Glycogen Synthesis

Glucose comes into the cell. It gets trapped by glucokinase (hexokinase in skeletal muscle). The glucose destined for glycolysis, goes. But some of that glucose-6-phosphate gets transformed into glucose-1-phosphate. This tells the cell, "hey, this glucose should be stored." That glucose-1-phosphate is charged using **UTP**, becoming **UDP-glucose**.

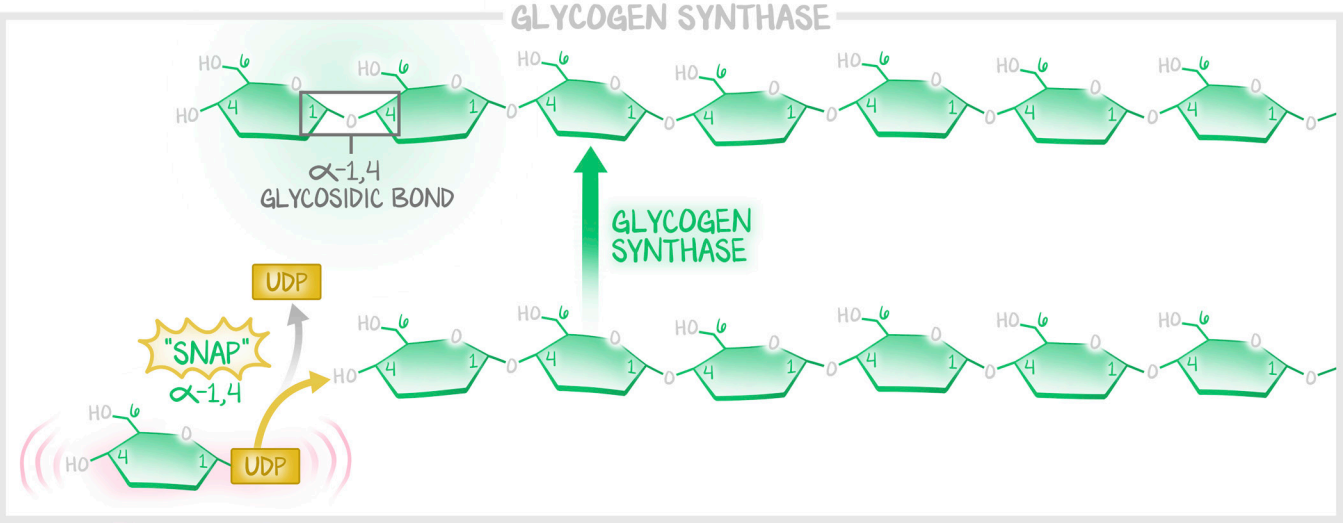

Figure 11.4: Glycogen Synthase
Glycogen synthase adds a glucose by taking a charged UDP-glucose and forming a 1,4 glycosidic bond.

Glycogen synthase, the rate-limiting step in this process, uses that high-energy UDP to make that **α-1,4-glycosidic bond**. Glycogen synthase does ONE thing. It elongates the chain—1,4 to 1,4 to 1,4 to 1,4, and so on. Glycogen synthase keeps elongating chains. Any time it finds a UDP-1-glucose free in the cytoplasm and a free 4 position of chain, SNAP, it puts them together. This is NOT sequential to the next step. It's occurring concurrently. **Branching enzyme** finds long straight chains made by glycogen synthase and makes them two straight chains, one new one "branched" from the original. The branching enzyme is sloppy, because it doesn't have to be precise. It'll grab a straight chain of 4-8 glucose molecules, all connected 1,4 to 1,4 and so on. It cuts one of those 1,4 bonds, takes the whole chunk, moves down a few glucose molecules on that original chain, and makes a 1,6 bond. The result is a branched chain (~5 glucose molecules long) that a glycogen synthase can add to, AND the original chain, from the branch-point to the end (also ~5 glucose molecules long), which a glycogen synthase can add to. When either gets too long, branching enzyme does it again.

This is important—glycogen synthase can't add to one- or two-glucose-long chains. It needs a decent length to do anything. A branch-point messes it up. This is true of glycogen phosphorylase as well.

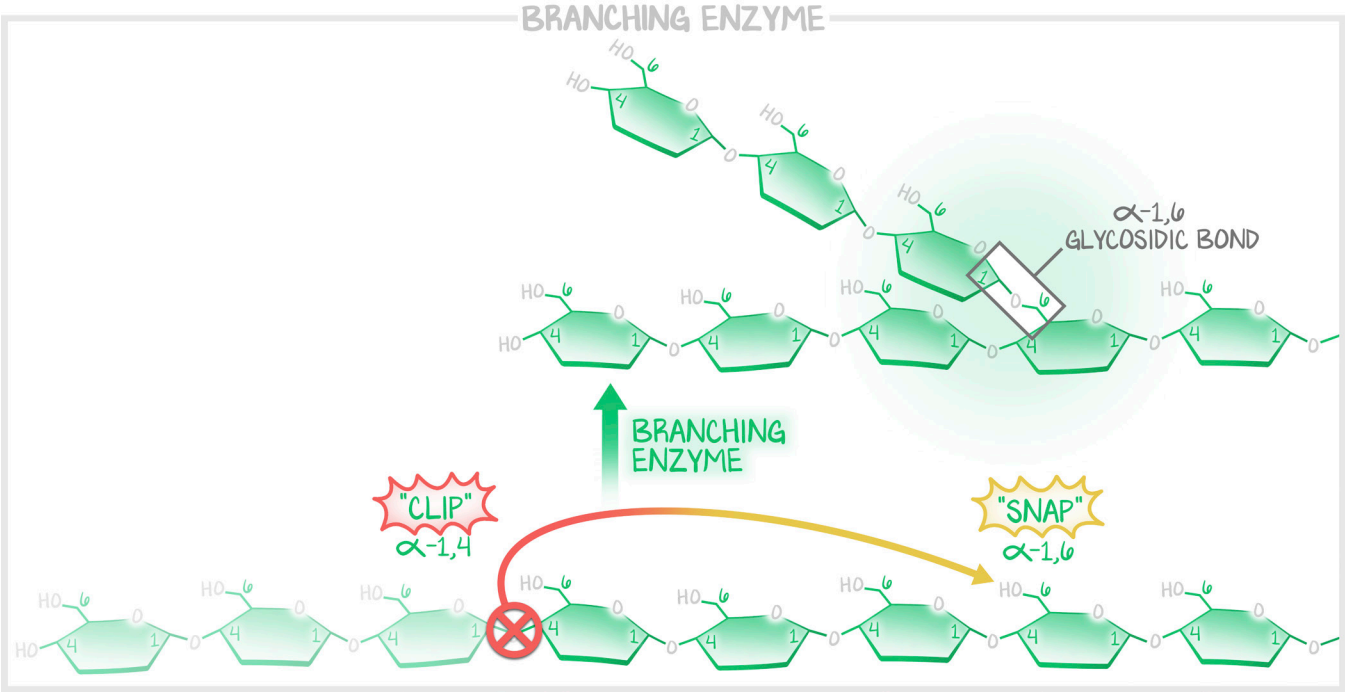

Figure 11.5: Branching Enzyme
Branching enzyme clips an already-elongated chain at the 1,4 position, moves a chunk of glucose molecules (connected to each other by 1,4 bonds) back down a bit on the chain, and attaches the two chains by a 1,6 bond.

Glycogenolysis

Glycogen phosphorylase comes up to the distal tips of the glycogen chains, as far from the core as possible. All these straight chains at the edge have an exposed glucose with a 1,4 bond. CLIP! A 1,4-glycosidic bond is broken and glucose-1-phosphate is released, which is then converted back to glucose-6-phosphate and burned (in muscle) or released (in liver).

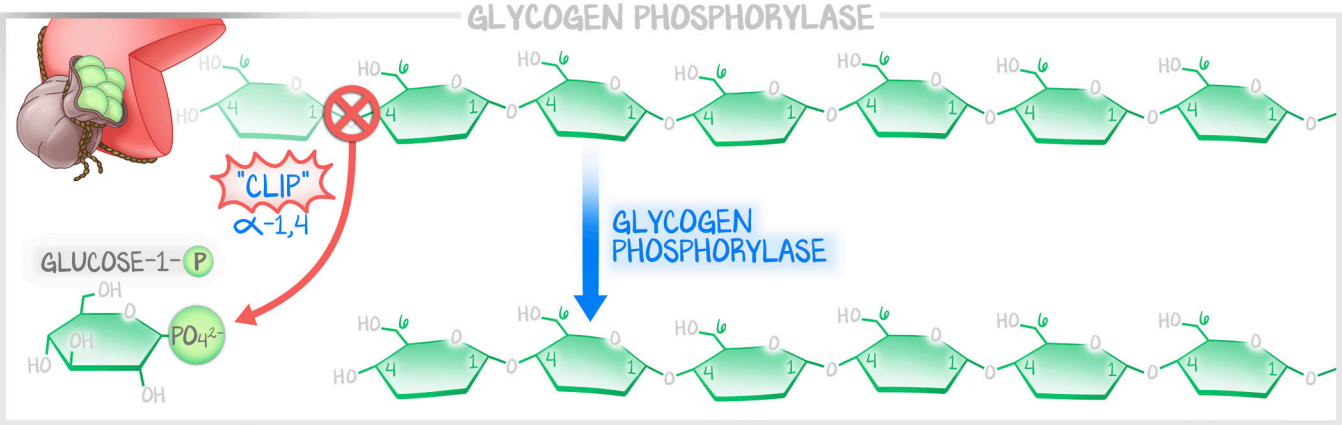

Figure 11.6: Glycogen Phosphorylase
Glycogen phosphorylase removes one glucose from the end of the straight chain, releasing a glucose-1-phosphate.

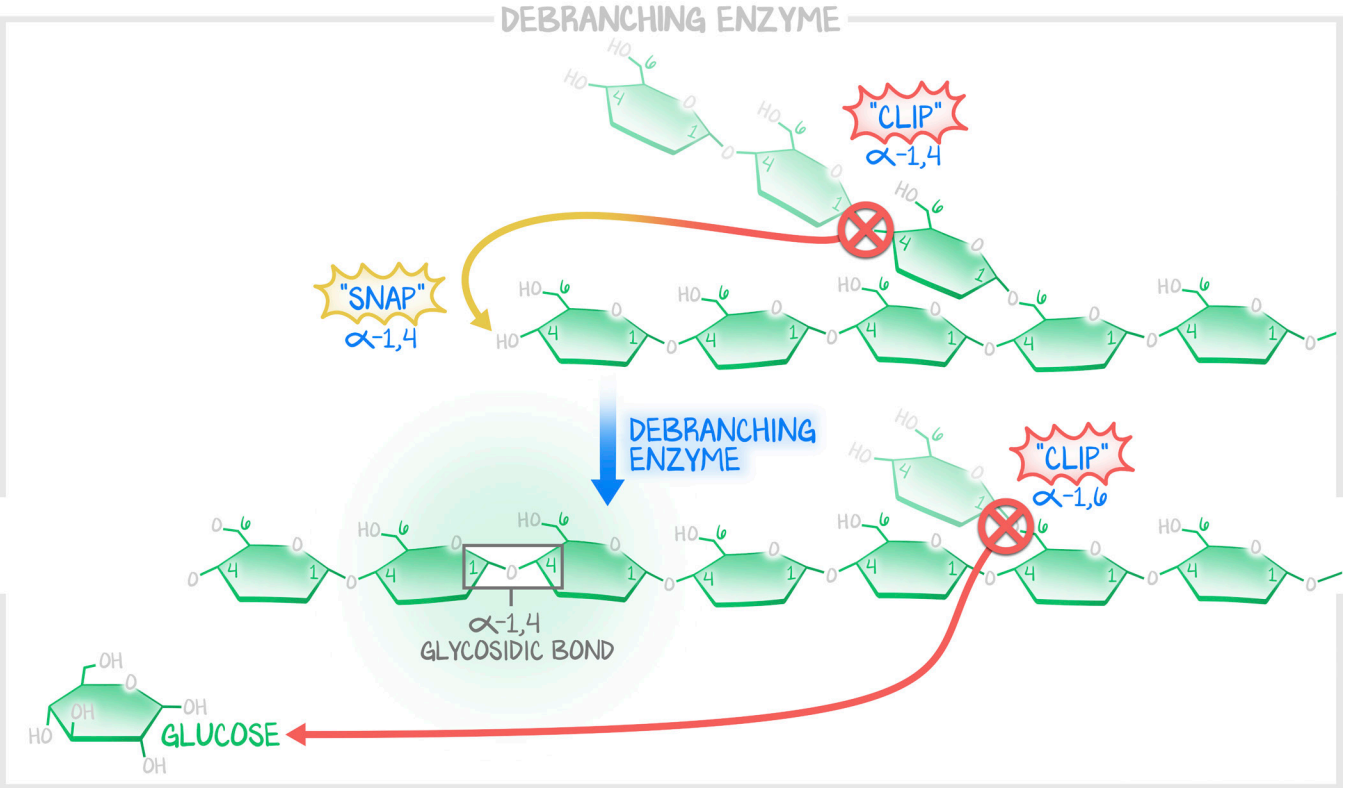

Figure 11.7: Debranching Enzyme
Debranching enzyme moves a strand that is branched by the 1,4 position, makes a 1,4 bond, then goes back to remove the 1,6 bond. This cleavage allows glycogen phosphorylase to continue its work (glucose-1-phosphate) but also debranching enzyme releases a single glucose molecule that is NOT phosphorylated.

But when glycogen phosphorylase gets too close to a branch, it can't work. So a **debranching enzyme** comes in and undoes, sort of, what the branching enzyme did. Be careful with the numbers. The debranching enzyme makes a cut in a **1,4 bond** of the branched chain. It takes the chunk and adds it to the chain the phosphorylase was working on. Clipping the 1,4 of the branch means that the 1,6 is still intact. The debranching enzyme leaves a glucose behind with a 1,6 bond! Don't worry, it knows. The debranching enzyme also **hydrolyzes the 1,6**, releasing a **free**, **unphosphorylated glucose** into the cytoplasm.

That means debranching "clips" 1,4, then "snaps" 1,4, then goes back and "clips" 1,6.

Regulation Is Both Hormonal and Substrate Level

Insulin brings glucose into the cell. It makes glucose-6-phosphate happen more often. Since glucose-6-phosphate is a substrate in glycogen metabolism, it makes sense that **insulin stimulates glycogen synthase** (and also, therefore, branching enzyme). At the same time it tells cells to take up glucose from the blood (GLUT4), it also tells the cells to use that glucose (glycolysis), and because the cell doesn't want to run out later, **to store glucose as glycogen**.

If insulin is pro-glycogen storage, then it's not surprising that **glucagon stimulates glycogen phosphorylase**. Glycogen phosphorylase, however, needs to work in certain tissues all the time, even if the whole body is insulin-dominant. Running from that T. rex can't wait for your sugar to drop and glucagon to rise. So, when it's needed, glycogen can be accessed locally (in a given muscle) under the influence of both **epinephrine** (the "hurry up and release" signal that goes systemically) and in **active tissue running out of energy**. Cells that are low on energy are high in **AMP**. A rise in AMP stimulates glycogen phosphorylase (and debranching enzyme).

ENZYME	FUNCTION	REGULATION
Glycogen synthase (**rate-limiting**)	Make α-1,4 bond to stack glucose molecules using charged UDP-glucose molecules	+ by ↑ insulin + by ATP, NADH, FADH2
Branching enzyme	Cut α-1,4, make branch via α-1,6	
Glycogen phosphorylase (**rate-limiting**)	Cut α-1,4, release glucose-1-phosphate	+ by ↑ **glucagon** + by ↑ **epinephrine** + by ↓ insulin + by ↑ **AMP** (ADP, NAD, FAD)
Debranching enzyme	Make room for glycogen phosphorylase: Cut α-1,4 of branch Add α-1,4 to main strand Cut remaining α-1,6 on branch, release **1** glucose-OH	+ by ↑ **AMP**

Table 11.1